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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/586,235	HASAN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003 and 13 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-16, 26, and 28-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-16,26 and 28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Exhibit I*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 24, 2003 has been entered.

2. The amendment filed September 22, 2003 has been entered. Claims 18-25 have been canceled. Claims 1-5, 7, 8, 10-16, and 26 have been amended. Claims 29-33 have been added.

3. The supplemental response filed February 13, 2004 is acknowledged and has been entered.

4. Claims 1-5, 7-16, 26, and 28-33 are pending in the application and are currently under prosecution.

Grounds of Objection and Rejection Withdrawn

5. Unless specifically reiterated below, the grounds of objection and/or rejection set forth in the previous Office action mailed May 20, 2003 have been withdrawn.

Response to Amendment

6. In the "Remarks" of the amendment filed September 22, 2003, Applicant has stated copies of press releases for rituximab and Herceptin™ have been submitted therewith. However, as copies of the press releases appear not to have been provided, the press releases have not been considered.

Reply to Supplemental Response

7. In the Supplemental Response filed February 13, 2004 Applicant has traversed the rejection of claims 1-4, 6-8, and 10-15 under 35 USC § 103(a) as being unpatentable over Ortel et al. and Momma et al. in view of Mueller et al. and Santini et al. Applicant has argued Ortel et al. is not a prior art document under 35 USC § 102(a) or (b), because Applicant has provided declaratory evidence under 37 CFR § 1.132 that Ortel et al. is not the work of others, as would be required of prior art under 35 USC § 102(a), and because Applicant has provided objective evidence in the attached Exhibit A that the issue of the journal in which Ortel et al. is published was not publicly accessible prior to one year before the filing date sought by Applicant in the instant application.

As explained in the advisory action mailed December 3, 2003, using available resources the Examiner was unable to confirm Applicant's statement that the publication date of Ortel et al. is June 10, 1998. To the contrary, Julia Maidment of the British Journal of Cancer Editorial Office states in a letter dated November 24, 2003, a copy of which letter is attached to the advisory action, that subscribers of the journal could have received the June 1998 issue as early as May 22nd or May 23rd of 1998. Accordingly, the advisory action invited Applicant to submit objective evidence that the issue of the journal in which Ortel et al. is published was not mailed by the publisher and/or not received by subscribers prior to one year to the date of the filing date sought by Applicant in the instant application. The objective evidence that Applicant has now provided as Exhibit A demonstrates in a single, possibly unique instance, contrary to the publisher's indications of November 24, 2003, the issue of the journal in question was not made publicly accessible earlier than one year prior to the filing date sought by Applicant. Attached hereto and marked as Exhibit I is supplemental evidence confirming and expanding upon the publisher's initial indications of November 24, 2003 that the issue of the journal in which Ortel et al. is published was publicly accessible prior to one year before the filing date sought by Applicant in the instant application. The attached letter of March 23, 2004 states, "a significant number of copies would have been in the hands of UK and European subscribers by or before 22/23

May 1998 and that those closely associated with the journal would have had copies a couple of days earlier"; see attached Exhibit I. Thus, the letter of March 23, 2004 confirms the initial indications of the editors of the British Journal of Cancer that Volume 77, Issue No. 11 was made publicly accessible more than one year before the filing date of the instant application. The letter of March 23, 2004 further states, "historically, the British Library has not always been able to make specialist journals and books publicly available on their publication date". Accordingly, the letter of March 23, 2004 suggests that although as Applicant has discovered, the British Library did not make the issue available to the public until on or after June 4, 1998, the inability of the British Library to make the issue accessible to the public on its publication date should not be construed as evidence that the journal was not mailed by the publisher and/or not received by subscribers prior to one year to the date of the filing date sought by Applicant in the instant application.

In further reply, if Ortel et al. were prior art under 35 USC § 102(a), as opposed to prior art under § 102(b), as stated in the advisory action mailed December 3, 2003, the declaration under 37 CFR § 1.132 by Tayyaba Hasan, Bernhard Ortel, and Edward Maytin filed September 22, 2003 is insufficient to overcome the rejection of claims the rejection of claims 1-4, 6-8, and 10-15 under 35 USC § 103(a) as being unpatentable over Ortel et al. and Momma et al. in view of Mueller et al. and Santini et al. for the reason stated in section 17 of the Office action mailed May 20, 2003.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-5, 7-13, and 18-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a method for inhibiting proliferation of a cancerous cell in a subject, wherein said method comprises

administering to a subject an agent that induces differentiation of a cancerous cell in a subject and further comprises administering to the subject 5-aminolevulinic acid (ALA), wherein the induction of differentiation in the cancerous cell is positively correlated with accumulation of intracellular ALA-induced protoporphyrin IX, does not reasonably provide enablement for a method for inhibiting cancerous cell proliferation in a subject comprising inducing differentiation of a cancerous cell in a subject and providing said cell with a photosensitizer comprising a porphyrin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant has traversed this ground of rejection set forth in section 8 of the Office action mailed May 20, 2003 arguing the following:

(a) Photodynamic therapy and differentiation therapy are well known modalities for treating cancer; the invention relates to the discovery that the combination of both modalities enhances the inhibition of cell proliferation, as compared to either modality alone. Since the level of skill in practicing the individual modalities is high, the skilled artisan could use the claimed invention to inhibit the proliferation of a cancerous cell in a subject without need of performing an undue amount of additional experimentation.

(b) Applicant cannot be expected to exemplify and provide data for every type of condition that can be treated using the claimed invention, because only an enabling disclosure is required and Applicant need not describe all actual embodiments.

(c) The claims do not encompass methods for inhibiting the proliferation of any cell, but are limited to cells undergoing cancerous proliferation.

(d) At pages 2 and 3, the specification lists photosensitizers that can be used in practicing the claimed invention. The mechanism by which a differentiating agent causes increased accumulation of protoporphyrin need not apply to all photosensitizing agents or precursors thereof, as the inventor does not need to comprehend the scientific principles on which practical effectiveness of his invention rests. It is irrelevant how a differentiation agent causes cells to differentiate.

(e) One of skill in the art could choose a differentiating agent, depending upon the identity of the target cell, without need to perform an undue amount of additional experimentation.

(f) The FDA has approved, and clinical trials have proven the effectiveness, the use of rituximab and Herceptin™. Monoclonal antibodies suitable for targeting particular cells are well known. The specification need not disclose and preferably omits that which is well known.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

(a) Applicant has argued since photodynamic therapy and differentiation therapy are well known modalities for treating cancer, and the level of skill in practicing the individual modalities is high, the skilled artisan could use the claimed invention to inhibit the proliferation of a cancerous cell in a subject without need of performing an undue amount of additional experimentation. In reply, the specification is enabling for using a method for inhibiting proliferation of a cancerous cell in a subject, wherein said method comprises administering to a subject an agent that induces differentiation of a cancerous cell in a subject and further comprises administering to the subject 5-aminolevulinic acid. However, the specification does not reasonably provide enablement for the scope of the claims drawn to a method for inhibiting cancerous cell proliferation in a subject comprising inducing differentiation of a cancerous cell in a subject and providing said cell with a photosensitizer comprising a porphyrin. Accordingly, in view of the rejections of claims under 35 USC §§ 102 and 103 set forth below, the embodiments of the claimed invention, which are novel and/or unobvious and not well known in the art, are the subject of this rejection.

Once again, the factors to be considered in determining whether undue experimentation would be required to practice the claimed invention are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and

the quantity of experimentation which would be required in order to practice the invention as claimed.

As stated in the Office action mailed May 20, 2003, the amount of guidance, direction, and exemplification provided in the disclosure is not reasonably commensurate with the scope of the claims and insufficient to enable the skilled artisan to practice the claimed invention with a reasonable expectation of success without the need to perform additional, undue experimentation. Furthermore, the declaration under 37 CFR § 1.132 by Dr. Ortel filed August 27, 2002 fails to provide a showing of evidence that is reasonably commensurate in scope with the claims. While the declaration under 37 CFR § 1.132 by Dr. Ortel states that the combination of differentiation therapy and photodynamic therapy is more effective than either therapy alone, the showings are limited to studies of an androgen-responsive prostate cancer cell line and a transplantable mammary sarcoma and are therefore not reasonably commensurate in scope with the claims.

As noted in the Office action mailed May 20, 2003, the declaration by Dr. Ortel does not, nor does the specification, provide a showing that the invention can be practiced to successfully treat a subject having an androgen-independent prostate cancer, which is not responsive to treatment with androgen. One skilled in the art would not expect the combination of differentiation therapy and photodynamic therapy to be more effective than either therapy alone in treating a patient diagnosed with androgen-independent prostate cancer in cases where the patient is treated with androgen, a known differentiating agent, because the cancer would not be expected to respond to androgen treatment and there is no reason to expect that treatment of the cancer with androgen would promote the increased accumulation of photoactive porphyrin in the cells following their exposure to ALA. In previously traversing this ground of rejection, Applicant argued the skilled artisan would not try to treat androgen-independent, or – non-responsive prostate cancer with the claimed invention. Even so, the present claims are drawn to a method for inhibiting the proliferation a cancerous cell comprising inducing in a subject differentiation of a cancerous cell, which cancerous cell can be an androgen-independent cancerous cell.

Now, Applicant has argued the invention relates to the discovery that the combination of both modalities enhances the inhibition of cell proliferation, as compared to either modality alone; yet, the teachings of Momma et al. (*International Journal of Cancer* 72: 1062-1069, 1997) suggest the application of the claimed invention is not amenable to the inhibition of proliferation of hormone non-responsive prostate tumor cells. Hormone non-responsive prostate tumor cells are no more effectively inhibited by the combination than by the single modality of photodynamic therapy alone, since differentiation therapy of the hormone non-responsive prostate cancer cell line does not cause increased accumulation of protoporphyrin as it does of the hormone-responsive prostate cancer cell line; see, e.g., the abstract, Figure 1, and page 1068, column 1. The specification fails to provide guidance and direction as to which differentiating agent is best suited for use in practicing the claimed invention to inhibit the growth of androgen-independent prostate cancer in a subject; accordingly, the specification fails to provide an enabling disclosure of the claimed invention, as required under 35 USC § 112, first paragraph.

The synthetic androgen R1881 increases the amount of protoporphyrin that accumulates in LNCaP cells, but as noted previously, other hormonal agents fail to have the same effect. Momma, et al (cited *supra*) teaches while dihydrotestosterone, like R1881, increases the cellular content of protoporphyrin, another hormonal agent, namely estradiol fails to do so (page 1064, column 1). It is further noted herein that the teachings of Siboni et al. (*Cancer Letters* **196**: 57-64, 2003) provide additional objective evidence that the skilled artisan cannot predict whether any given differentiating agent can be used to induce the differentiation of any type of cancerous cell, such that the differentiated cancerous cell might be expected to preferentially accumulate any given photosensitizing agent. Siboni et al. teaches specific cell differentiation of colon cancer cells by the differentiating agent sodium butyrate results in reduced accumulation of endogenous protoporphyrin IX after exposure of the cells to ALA (abstract). Thus, the teachings of Siboni et al. demonstrate that not just any differentiating agent can be used to induce the differentiation of a particular type of cancerous cell, such that the differentiated cell preferentially accumulates the ALA-induced photosensitizer

protoporphyrin. In other words, given the teachings of Siboni et al., it is not reasonable to presume that any differentiating agent, which induces the differentiation of a particular type of cancerous cell, can be used in combination with any one photosensitizing agent to have a reasonable expectation of success in practicing the claimed invention.

This conclusion is further supported by the teachings of Li et al. (Photochemistry and Photobiology 69: 231-235, 1999). Li et al. teaches the accumulation of abnormally large amounts of protoporphyrin by some types of cancer cells following their exposure to the differentiating agent dimethylsulfoxide (DMSO) is cell-type specific (abstract). Li et al. demonstrates this point by showing that the human promyelocyte cell line HL-60 accumulates *less* protoporphyrin after inducing the cells to differentiate upon exposure to DMSO than before (abstract). In contrast, Li et al. show that the mouse preadipocyte cell line 3T3 L1 accumulates more protoporphyrin after exposure to DMSO than before (abstract). Thus, it cannot be predicted whether a given type of cell will respond favorably to treatment by a differentiating agent to accumulate more or less protoporphyrin.

Further regarding the choice of an appropriate differentiating agent, Ortel et al. (*British Journal of Cancer* **87**: 1321-1327, 2002) teaches, "[t]he success of our approach, using cellular differentiation to modulate ALA-PDT [ALA-mediated photodynamic therapy], *depends* upon the availability of suitable differentiation-modulating agents that work in the tumor of interest" (italicized for emphasis) (page 1326, column 1). Ortel et al. also teaches, "differentiation may not enhance PpIX [protoporphyrin IX] formation in all cells and tumour types" (page 1326, column 1). In reference to the teachings of Li et al. (cited *supra*), Ortel et al. discloses dimethylsulfoxide (DMSO), which induces differentiation of HL-60 cells, fails to cause an increased accumulation of intracellular protoporphyrin by the cells (page 1326, column 1). Accordingly, Ortel et al. concludes, "not all cell-types may be amenable to DT [differentiation therapy] as a way to augment the efficacy of ALA-PDT" (page 1326, column 1); and regarding the potential caveats of their findings, Ortel et al. discloses, "DT actually decreased the inherent cellular sensitivity to PDT" of differentiated cells,

relative to undifferentiated cells, which contained similar levels of protoporphyrin (page 1326, column 2). Thus, the teachings of Ortel et al. further support the Office's position that the amount of guidance, direction, and exemplification disclosed by Applicant would not be sufficient to enable the skilled artisan to select a differentiating agent, which can be used in combination with a photosensitizing agent to have a reasonable expectation of successfully inhibiting the proliferation of any type of cancerous cell in a subject without the need to first perform an undue amount of additional experimentation.

Claim 29 is drawn to the method of claim 10, wherein retinoic acid is provided in an amount sufficient to induce differentiation; claim 30 is drawn to the method of claim 11, wherein troglitazone or transcription factor PPAR gamma is provided in an amount sufficient to induce differentiation; and claim 31 is drawn to the method of claim 12, wherein wherein an androgen, a retinoid, vitamin D, or liazorole is provided in an amount sufficient to induce differentiation. As noted in the Office action mailed May 20, 203, Mueller et al. teaches that antidiabetic compounds, namely the thiazolidinediones, such as troglitazone, induce the terminal differentiation of breast cancer cells; Santini et al. teaches treatment of a patient diagnosed with the hematopoietic cell malignancy promyelocytic leukemia with all-*trans*-retinoic acid (ATRA) is the paradigm of differentiation therapy; and the specification shows that R1881, a synthetic androgen, can be used to induce the differentiation of prostate cancer cells. Accordingly, it is appreciated that troglitazone, retinoic acid, and R1881 can be used to induce the differentiation of different types of cancerous cells, but apart from the use of R1881 in combination with ALA-mediated photodynamic therapy to inhibit the proliferation of androgen-dependent prostate cancer cells, it cannot be predicted whether any of the other differentiating agents disclosed in the specification and/or recited in the claims can be used in combination with a particular photosensitizing agent to successfully practice the claimed invention. Therefore, in order to have a reasonable expectation of success, the skilled artisan would first have to perform an undue amount of additional experimentation to determine which, if any of the differentiating agents, including troglitazone and retinoic acid, can be used in combination with a selected photosensitizing agent.

In addition, the present claims encompass the use of a rather broad genus of photosensitizers, which photosensitizers "comprise" a porphyrin; yet, the specification only demonstrates the use of a single photosensitizing agent, namely 5-aminolevulinic acid (ALA), which is a metabolic heme precursor converted intracellularly to protoporphyrin IX. Krieg et al. (*Photochem. Photbiol.* **76**: 518-525, 2002) teaches the preferential accumulation of protoporphyrin IX (PPIX) by tumor cells is strongly influenced, but not solely determined, by the activity differences between the PPIX-producing porphobilinogen deaminase and the PPIX-converting ferrochelatase, as compared to fibroblasts, but the tumor-specific accumulation is generated by ALA conversion rather than by initial uptake (abstract). It is known the expression of, and therefore the activity of, these enzymes is regulated in a differentiation-specific manner. For example, Magness et al. (*Blood* **95**: 3568-3577, 2000) teaches ferrochelatase expression is unregulated during differentiation of primitive erythroid cells (abstract). Therefore, it appears the predominant mechanism by which a differentiating agent causes increased accumulation of protoporphyrin in cells induced to differentiate relative to control cells involves the increased expression of, or activity of ferrochelatase and porphobilinogen deaminase, enzymes that participates in the biosynthesis or conversion of ALA into protoporphyrin. However, absent a showing of any factual evidence in support, it would be unreasonable to expect other photosensitizers or precursors thereof will accumulate preferentially in differentiated cancer cells because accumulation of other photosensitizers is not be dependent upon the expression or activity of such enzymes. For example, it is not expected that hematoporphyrin derivatives, e.g., Photofrin™, will preferentially accumulate in differentiated tumor cells relative to non-differentiated tumor cells. Hematoporphyrin derivatives are not synthesized or converted from a precursor by an enzyme, such as ferrochelatase, which is regulated in a differentiation-specific manner; and there appear to be no reports that hematoporphyrin derivatives are selectively taken up by differentiated tumor cells relative to non-differentiated tumor cells. To the contrary, Momma et al. (cited *supra*) teaches the uptake and/or accumulation of benzoporphyrin derivative-monoacid ring A (BPD-MA), which is an "exogenous" photosenstizer, such as chlorin e6 and other

hematoporphyrin derivatives, unlike "endogenous" photosensitizer protoporphyrin IX, does not increase in differentiated cells, as compared to undifferentiated cells. Absent a showing that is reasonably commensurate in scope with the claims, the skilled artisan would not accept the assertion that any photosensitizer will accumulate preferentially in a cancer cell upon the induction of its differentiation, regardless of which differentiating agent has been used. Notably, the specification has not provided objective evidence that exogenous photosensitizers, such as chlorin e6 can be used in place of ALA-induced protoporphyrin in practicing the claimed invention.

Further regarding claim 30, which recites providing an amount of PPAR gamma, which is sufficient to induce differentiation, the specification does not provide teach how the required amount of PPAR gamma can be provided. At page 18, lines 25 and 26, the specification discloses ligands of PPAR gamma induce differentiation, but there is no guidance as to how a sufficient amount of PPAR gamma might be provided to induce differentiation. Given the benefit of Applicant's disclosure, the skilled artisan might envision providing PPAR gamma by gene transfer, or *gene therapy*; however, the art of gene therapy, i.e., the *in vivo* delivery genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, is still in its infancy. Moreover, the art is highly unpredictable and its successful application has been hindered by numerous limitations, which the specification does not remedy and would preclude the skilled artisan from having a reasonable expectation of successfully making and using the claimed invention without need of performing an undue amount of experimentation. For example, the teachings of the specification have not overcome the problems with *in vivo* delivery and expression. Verma et al. (*Nature* 1997, **389**: 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al. state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression. Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, **2**: 111-133) teach that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies. In addition, Amalfitano et al. discuss numerous limitations that have been encountered in using retroviral vectors to deliver DNA into a subject and teach the use of adenoviral vectors can be ineffective because of the induction of strong

immune responses in the host to the viral vectors and direct acute and chronic toxicity caused by the vector itself. Considering the state of the art, the skilled artisan could not have a reasonable expectation of successfully practicing the claimed invention without the need to perform an undue amount of additional experimentation.

The specification reviews "coupling technologies" at pages 14-18. Nevertheless, regarding claim 28, which is drawn to the method of claim 26 wherein ALA is coupled to a targeting moiety, conjugates of ALA and targeting moieties, including antibodies, appear not to be well known in the art. Notably the specification does not teach methods by which ALA can be conjugated to a targeting moiety, such that the resulting conjugate retains the ability of ALA to be selectively taken up by differentiated tumor cells and metabolized intracellularly to form protoporphyrin. Since uptake of the conjugate will depend upon the binding of the targeting moiety to a targeted cell, the uptake of the conjugate will mechanistically differ from the uptake of unconjugated ALA, such that one cannot reasonably extrapolate the examples given in which ALA is not conjugated to predict the effectiveness of the claimed method. In addition, it would be necessary to select a targeting moiety that is efficiently internalized by the cell, since unless the conjugate is internalized, ALA cannot be converted into protoporphyrin. However, not all antibodies, for example, are internalized, so only certain antibodies might be used to practice the claimed invention. Yet, the specification provides no guidance as to how antibodies, which can be used to practice the claimed invention, might be selected and coupled to ALA without preventing its conversion to protoporphyrin once it has been internalized.

(b) Applicant has argued it is not necessary to exemplify every embodiment of the claimed invention. Applicant is correct; however, while it is not necessary to exemplify every embodiment of the claimed invention, Applicant's must provide a showing that is reasonably commensurate in scope with the claims and that showing must be sufficient to enable the skilled artisan to have a reasonable expectation of successfully practicing the claimed invention without need of performing an undue amount of additional experimentation. The preponderance of objective evidence set forth herein supports the Office's position that the amount of guidance, direction, and

exemplification is not reasonably commensurate in scope with the claims and would not be sufficient to enable the use of the claimed invention as required by 35 USC § 112, first paragraph.

(c) Applicant has argued the present claims do not encompass methods for inhibiting the proliferation of any cell, but are limited to cells undergoing cancerous proliferation. Actually, claims 1-5, 7-13, 26, and 28-31 are drawn to a method for inhibiting the proliferation of a cancerous cell in a subject, not to a method for inhibiting cells undergoing cancerous proliferation. Nonetheless, presently 1-5, 7-13, 26, and 28-31 encompass methods for inhibiting the proliferation of any type of cancerous cell in a subject. However, exemplification of the claimed invention is limited to methods wherein the cancerous cell is an androgen-dependent prostate cancer cell line, the photosensitizing agent is ALA, and the differentiating agent is R1881; and the amount of guidance, direction, and exemplification is not reasonably commensurate in scope with the claims, since the amount of guidance and direction is not sufficient to enable the skilled artisan to select a combination of photosensitizing agent and differentiating agent, which can be used effectively to treat at least a substantial number of the different types of cancer.

(d) Applicant has argued the list of photosensitizers at pages 2 and 3 of the specification would be sufficient guidance to enable the skilled artisan to select a particular photosensitizing agent, which can be used effectively in combination with a particular differentiating agent to treat at least a substantial number of the different types of cancer, since the mechanism by which a differentiating agent causes increased accumulation of protoporphyrin need not apply to all photosensitizing agents or precursors thereof, the inventor does not need to comprehend the scientific principles on which practical effectiveness of his invention rests, and it is irrelevant how a differentiation agent causes cells to differentiate. In reply, while it is irrelevant just how a differentiation agent causes a cancerous cell to differentiate, it is not irrelevant how a given cancerous cell differentiates in response to a particular differentiating agent, depending upon which photosensitizing agent is to be used in the combination. In view of the objective evidence set forth herein, it is reasonably expected only certain

differentiating agents can be used to induce the differentiation of the a particular type of cancerous cell, such that the differentiated cancerous cell preferentially accumulates a selected photosensitizing agent. The skilled artisan cannot predict whether a given differentiating agent will cause the differentiated cell to preferentially accumulate a given photosensitizing agent; and therefore, without the need to perform an undue amount of additional experimentation, the skilled artisan could not practice the claimed invention with a reasonable expectation of success. Therefore, while the mechanism by which some differentiating agents, e.g., DMSO, cause increased accumulation of intracellular protoporphyrin need not apply to all photosensitizing agents or precursors thereof, the skilled artisan cannot predict whether a mechanism by which a given differentiating agent causes the preferential accumulation of a given photosensitizing agent actually exists. Therefore, absent empirical determinations, the skilled artisan cannot know whether any particular combination of photosensitizing agent and differentiating agent can be used effectively to inhibit the proliferation of any particular type of cancerous cell in a subject.

(e) Applicant has argued one of skill in the art could choose a differentiating agent, depending upon the identity of the target cell, without need to perform an undue amount of additional experimentation. While the skilled artisan could select a differentiating agent, which is known or might be reasonably expected to induce the differentiation of a particular type of cancerous cell in a subject, as explained above, the skilled artisan the skilled artisan cannot know, or even predict whether any particular combination of photosensitizing agent and differentiating agent can be used effectively to inhibit the proliferation of any particular type of cancerous cell in a subject, because only certain differentiating agents are expected to cause the preferential uptake and accumulation of a given photosensitizing agent by the cancerous cell. The amount of guidance and direction set forth in the specification would not be sufficient to enable the skilled artisan to select a combination of photosensitizing agent and differentiating agent can be used effectively to inhibit the proliferation of any particular type of cancerous cell in a subject. Therefore, the disclosure is not sufficiently enabling of the use of the

claimed invention to meet the requirements set forth under 35 USC § 112, first paragraph.

(f) With regard to claims 9 and 28, in particular, Applicant has argued monoclonal antibodies suitable for targeting particular cells are well known; since the specification need not disclose and preferably omits that which is well known, the disclosure should be viewed as sufficiently enabling the use of the claimed invention to meet the requirements set forth under 35 USC § 112, first paragraph. Claim 9 is drawn to the method of claim 1 wherein the photosensitizer is coupled to a targeting moiety; claim 28 is drawn to the method of claim 26 wherein 5-aminolevulinic acid (ALA) is conjugated to a targeting moiety; and at page 14, the instant disclosure contemplates the use of a monoclonal antibody as a targeting moiety. It is duly noted that while before Applicant argued since the targeting agent of claim 9 is not used to ameliorate or inhibit tumors, any reliance upon the references teaching the limitations of monoclonal antibodies and other tumor-antigen targeted therapies is misguided, because claim 1 now recites a method of *inhibiting* cancerous cell proliferation, the reliance upon such references to support the Office's position should now be considered astute. As set forth in the previous Office action mailed May 20, 2003, Vitetta et al. teaches limitations associated with the use of monoclonal antibody-mediated therapy, which contrary to Applicants' previous assertion, are duly expected to affect the efficacy of the claimed invention, even if the antibody, itself, is not cytotoxic or cytostatic in nature. In addition, Bodey et al. teaches cancer cells expressing the antigens that are targeted by monoclonal antibodies are often "deselected", which further supports the Office's position that the amount of guidance, direction, and exemplification disclosed by Applicant would not be sufficient to enable the skilled artisan to have a reasonable expectation of successfully practicing the claimed invention to inhibit the proliferation of a cancerous cell in a subject without need of performing an undue amount of additional experimentation. Applicant has implied since the Food and Drug Administration (FDA) has approved the use of particular monoclonal antibodies, e.g., Herceptin™ and rituximab to treat cancer and clinical trials have proven these drugs effective, the limitations associated with monoclonal antibody-mediated therapy have been overcome.

However, the approval by the FDA of Herceptin™, for example, to treat breast cancer and its proven effectiveness does not change the fact that even given the benefit of Applicant's disclosure, the skilled artisan could not have a reasonable expectation of success in practicing the claimed invention to inhibit the proliferation of a cancerous cell in a subject without need of having to first perform an undue amount of additional experimentation. The amount of guidance, direction, and exemplification disclosed by Applicant is not reasonably commensurate in scope with the claims; nor would it be sufficient to enable the use of the claimed invention by the skilled artisan in accordance with the requirements set forth under 35 USC § 112, first paragraph. Claim 1 presently encompasses methods for inhibiting the proliferation of any type of cancerous cell in a subject; while the use of Herceptin™, for example, has been approved by the FDA to treat breast cancer that overexpresses HER-2/erbB2 and has been proven effective, monoclonal antibodies capable of effectively targeting any and all types of cancer have yet to be identified. Notably, the use of Herceptin™ has not been approved for use in treating breast cancer that does not overexpress HER-2/erbB2, since Herceptin™ lacks efficacy when the breast cancer does not abundantly express HER-2/erbB2; see the full prescribing information for Herceptin™, which has been cited on the attached PTO-Form 892. Furthermore, Herceptin™, which is a humanized version of mouse monoclonal antibody 4D5, cannot be used to treat other types of cancer, regardless of whether or not HER-2/erbB2 is overexpressed. Lewis et al. (*Cancer Immunology & Immunotherapy* **37**: 255-263, 1993) teaches that gastric and colon carcinoma cell lines are completely resistant to treatment with the monoclonal antibody 4D5, despite the fact that the gastric and colon carcinoma cells lines express amounts of the HER receptor that are equivalent to the amount expressed by breast cancer cell lines, which are sensitive to the inhibitory effect of the monoclonal antibody (page 259, column 2). Accordingly, the presence of an antigen, and even its overexpression at the surface of a cancerous cell, cannot be used as an indication that an antibody that binds the antigen can be used effectively to inhibit the proliferation of that cell. Thus, contrary to Applicant's argument, the approval of Herceptin™ or rituximab by the FDA and their

proven effectiveness in treating a particular type of cancer cannot be construed as factual evidence the skilled artisan would have a reasonably expectation of success in practicing the claimed invention to inhibit the proliferation of any type of cancer by conjugating a photosensitizer to an antibody that targets that type of cancer without need of first performing an undue amount of additional experimentation.

10. Claims 5, 7, 8, 9, 16, 26, and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(a) Claims 5 and 16 recite "a chlorin derivative". Claim 5 is drawn to a method for inhibiting cancerous cell proliferation in a subject comprising providing a cancerous cell with a member of the genus consisting of chlorin derivatives. Despite the issue under 35 USC § 112, second paragraph set forth below, claim 16 is interpreted to be drawn to a method for detecting cell proliferation in a subject comprising providing a cell with a member of the genus of chlorin derivatives. However, it cannot be determined what constitutes a chlorin derivative. At page 5, for example, the specification lists mono-1-aspartyl derivative of chlorin e6, but the specification does not include a written description of the genus, such that the skilled artisan could immediately recognize or distinguish members of the genus from others, because the specification does not describe the chlorin from which the chlorin derivatives are to be synthesized, nor does the specification describe how the parental chlorin molecule can be derivatized in forming the members of the genus of chlorin derivatives.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled

> in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991).

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

(b) Claim 7 recites "a compound which causes accumulation of the PS, formation of the PS, or is converted to the PS"; claim 8 recites "a compound which causes accumulation of, formation of, or is converted to a protoporphyrin"; and claim 26 recites "a compound that induces photosensitizer (PS) accumulation". In each instance, the claims refer to one or more genera of compounds; however, the members of each genus of compounds are merely described by a recitation of functional language. Presumably the members of the claimed genera of compounds are structurally diverse,

as the specification does not describe any structural feature that is common among at least a substantial number of members of each different genus. Accordingly, the members of the genus of targeting moieties must have a common functional attribute, but the functional attribute appears unrelated to the any common structural attribute. In deciding *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the Court held that a generic statement that defines a genus of nucleic acids, or by analogy, a genus of compounds *by only their functional activity* alone does not provide an adequate written description of the genus. The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus *is* achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members. Therefore, even given the benefit of Applicant's disclosure, the skilled artisan could not immediately recognize at least a substantial number of members of the various genera of compounds to which the claims refer. Accordingly, the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

(c) Claims 9 and 28 recite "a targeting moiety". At page 14, lines 1-19, the specification describes the genus of targeting moieties, which can be coupled to the photosensitizing agent when practicing the claimed invention. The specification discloses the targeting moiety can be a naturally occurring protein, a peptide, an antibody, and a ligand. Antibodies are well-characterized targeting moieties; however, antibodies are not representative of the genus of targeting moieties, as a whole, because antibodies are not representative of the subgenera of naturally occurring proteins, peptides, and ligands, the member of which can be used as a targeting moiety in practicing the claimed invention. The subgenera may overlap, but each subgenus is

reasonably expected to comprise structurally unrelated members. The specification merely describes the various members of the subgenera as having "specificity for one or more cell or tissue types, affinity and avidity for such targets, and stability with respect to conditions of coupling reactions and the physiology of the organ or tissue of use" (page 14, lines 2-3). Accordingly, the members of the genus of targeting moieties must have a common functional attribute, but the functional attribute appears unrelated to the any common structural attribute. Again, the Court has decided a generic statement that defines a genus of nucleic acids, or by analogy, a genus of targeting moieties *by only their functional activity* alone does not provide an adequate written description of the genus; see *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412). The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members. Therefore, even given the benefit of Applicant's disclosure, the skilled artisan could not immediately recognize at least a substantial number of members of the various subgenera of targeting moieties to which the claims refer. Accordingly, the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

In addition, while it is noted that at page 14 the specification describes some methods by which suitable targeting moieties might be identified or isolated for use, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, or for screening for it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

11. Claims 1-5, 7-16, 26, and 28-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 recites, "a photosensitizer (PS) *comprising* a porphyrin"; and claim 14 recites, "a light emitting agent *comprising* a porphyrin". At page 2, line 29, through page 3, line 19 and at page 5, line 10, through pager 6, line 2, the specification describes suitable photosensitizers and/or light emitting agents. While some of the photosensitizers and/or light emitting agents are "porphyrins", it does not appear that any of those recited in the specification would be described as "comprising a porphyrin". Accordingly, the recitation of the terms "a photosensitizer (PS) *comprising* a porphyrin" and "a light emitting agent *comprising* a porphyrin" appear to introduce new matter and thereby violates the written description requirement set forth under 35 USC § 112, first paragraph.

Claims 14-16 are drawn to a method for detecting cell proliferation in a subject comprising providing a differentiating agent to a cell of a subject and a control cell, providing the cells with a light emitting agent, activating said agent, and measuring light emission in the cells, wherein an increase in light emission from the differentiated cell of the subject relative to the control cell indicates the cell of the subject is proliferative. The specification provides written support for a method for detecting the presence of cell proliferative disorder, such as cancer, but the specification does not appear to provide adequate written support for the presently claimed invention. Therefore, the claims appear to introduce new matter and thereby violate the written description requirement set forth under 35 USC § 112, first paragraph.

Claim 26 recites, "[a] method for inhibiting androgen-dependent prostate cancer". At pages 20-22, the specification discloses examples in which LNCaP cells are used. LNCaP is an androgen-dependent prostate cancer cell line. Nevertheless, the disclosure of a single cell line, which is androgen-dependent, is not deemed sufficient to provide written support for the recitation "androgen-dependent prostate cancer" in claim 26, because the recitation excludes other types of prostate cancer, i.e., androgen-independent prostate cancer, which are not excluded or set apart from "androgen-dependent cancer" by any other disclosure. For example, at page 6, lines 15-18, the

specification discloses the cancerous cell can be a cancerous cell of the prostate, but the disclosure does not include any description of the androgen-dependency, or androgen-independency of the cancerous prostate cell. For this reason, the recitation of "androgen-dependent prostate cancer" in claim 26 appears to introduce new matter and thereby violates the written description requirement set forth under 35 USC § 112, first paragraph.

These matters might be resolved if Applicant were to point to specific disclosures in the specification, as originally filed, which are believed to provide proper and sufficient written support for the above mentioned recitations in the claims.

12. Claims 14-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 14-16 are drawn to a method for detecting cell proliferation in a subject comprising providing a differentiating agent to a cell of a subject and a control cell, providing the cells with a light emitting agent, activating said agent, and measuring light emission in the cells, wherein an increase in light emission from the differentiated cell of the subject relative to the control cell indicates the cell of the subject is proliferative.

Exposure of cells to differentiating agents often arrests cell proliferation and leads to terminal differentiation. For example, Ortel et al. (*British Journal of Cancer* **87**: 1321-1327, 2002) teaches exposure of LNCaP cells to the differentiating agent R1881 arrests cell proliferation and induces differentiation (page 1323, column 2). Ortel et al. teaches one should expect increased ALA-induced protoporphyrin accumulation in LNCaP cells induced to undergo differentiation by treatment with R1881, relative to control cells not so induced, because differentiated LNCaP cells preferentially accumulate protoporphyrin (page 1321, column 2). In this circumstance, following photoactivation of endogenous protoporphyrin, one should expect to observe increased light emission from the cell induced to differentiate, relative to a control cell, but the

increase in light emission would not be indicative that the cell is proliferative. In further support of this position, Momma et al. (*International Journal of Cancer* **72**: 1062-1069, 1997) teaches the cellular content of protoporphyrin does not correlate with growth rate (page 1066, column 2). Accordingly, while the change in light emission might be indicative that the cell of the subject is differentiated, it would not be indicative that the cell is proliferative.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-5, 7-16, 29, 30, and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 and 7-16 are indefinite because claims 1 and 14 recite the terms "a photosensitizer comprising a porphyrin" and "a light emitting agent comprising a porphyrin", respectively. Claim 5 recites, "[t]he method of claim 1, wherein the photosensitizer **is** chlorin e6 or a chlorin derivative", whereas claim 15 recites, "[t]he method of claim 14, wherein the light emitting agent **is** a protoporphyrin" (emboldened for emphasis). Since chlorin e6, a chlorin derivative, and protoporphyrin *are* "porphyrins", the meaning and breadth of the terms "a photosensitizer comprising a porphyrin" and "a light emitting agent comprising a porphyrin" is unknown. Therefore the metes and bounds of the claims cannot be determined.

Claim 16 is indefinite because the claim recites, "[t]he method of claim 14, wherein *the photosensitizer*" (italics added for emphasis). There is no antecedent basis in claim 14 to support the recitation of this limitation.

Claims 29, 30, and 31 are indefinite because claim 29 recites, "wherein retinoic acid is provided in an amount sufficient to induce differentiation", "claim 30 recites, "wherein troglitazone or transcription factor PPAR gamma is provided in an amount sufficient to induce differentiation", and claim 31 recites, "wherein an androgen, a retinoid, vitamin D or liarozole is provided in an amount sufficient to induce

differentiation". Although claims 10, 11, and 12, which depend from claim 1, recite, "inducing in a subject differentiation in a cancerous cell", it cannot be determined with reasonable certainty whether the amount of retinoic acid, troglitazone or transcription factor PPAR gamma, or androgen, retinoid, vitamin D or liarozole provided is sufficient to induce differentiation of the cancerous cell, some other cell, or perhaps any and every cell in a subject. 35 USC § 112, second paragraph requires the claims to particularly point out and distinctly claim the subject matter that applicant regards as the invention so that one might readily determine the metes and bound of the claimed invention.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

16. Claims 1-5, 7, 8, 11, and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 98/30242 A2.

WO 98/30242 A2 teaches a pharmaceutical composition for use in the treatment of disorders or abnormalities of the skin and other body surfaces by photochemotherapy (page 1, paragraph 1). WO 98/30242 A2 discloses the abnormalities and disorders that may be treated using the disclosed composition include any malignant or pre-malignant tumor or dysplasia of the skin or a body surface, including the lining of organs, such as the breast; see, e.g., page 16, paragraph 4, through page 18, paragraph 1. WO 98/30242 A2 teaches a preferred composition comprises 5-aminolevulinic acid (ALA), Photofrin™, and dimethylsulfoxide (DMSO) (page 14, paragraph 3). WO 98/30242 A2 teaches a synergistic effect has been observed, which results in enhanced efficiency of photodynamic therapy (PDT), when such a composition is used (page 14, paragraph 4). WO 98/30242 A2 discloses this effect enables the use of sub-therapeutic dosages, i.e.,

dosages which, were the individual photochemotherapeutic agent to be administered on its own, would not suffice to achieve a beneficial photochemotherapeutic effect (page 14, paragraph 4). WO 98/30242 A2 teaches chlorin e6 or m-THPC, a chlorin derivative, can be used in place of Protofrin™ (page 10, paragraph 2). WO 98/30242 A2 recognizes DMSO is a differentiating agent, which increases the activity of enzymes involved in heme biosynthesis, such that formation of protoporphyrin by cells is enhanced upon treatment with DMSO; see, e.g., page 11, paragraph 2, and page 12, paragraphs 2 and 3.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. As addressed above, Applicant has traversed any ground of rejection under 35 USC § 103(a) as being unpatentable over a combination of references that includes Ortel et al., including the ground of rejection set forth in section 17 of the previous Office action mailed May 20, 2003, by asserting that the declaration under 37 CFR § 1.132 by Tayyaba Hasan, Bernhard Ortel, and Edward Maytin filed February 28, 2003 excludes Ortel et al. from prior art under 35 USC § 102(a) and therefore overcomes any such grounds. For the reasons already stated above, Ortel et al. is regarded as prior art under § 102(b). Therefore, Applicant's arguments and the merit of the declaration have not been found persuasive or sufficient to overcome the grounds of rejection under 35 USC § 103(a) set forth below, which rely upon the teachings of Ortel et al. Nevertheless, upon further consideration in view of the present claims, the ground of rejection set forth in section 17 of the previous Office action mailed May 20, 2003 has been withdrawn.

19. Claims 1-4, 7, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ortel et al. (*British Journal of Cancer* **77**: 1744-1751, 1998), as evidenced by the attached letter of March 23, 2004 (Exhibit I).

The attached letter of March 23, 2004 (Exhibit I) provides evidence the issue of the journal in which Ortel et al. is published was publicly accessible prior to one year before the filing date sought by Applicant in the instant application, such that the reference qualifies as prior art under 35 USC § 102(b).

Ortel et al. teaches the cell line PC12, which is derived from a transplantable rat phaeochromocytoma, differentiates in response to treatment with nerve growth factor (NGF) (page 1749, column 2). Ortel et al. teaches, while the levels of protoporphyrin in PC12 cells treated with ALA alone were below the detection limit, the NGF-induced differentiation of the cells leads to accumulation of protoporphyrin (paragraph bridging pages 1749 and 1750). Ortel et al. concludes, "more differentiated tumours or chemotherapy-insensitive tumours with slowly cycling cells may be the better targets of ALA-dependent PDT [photodynamic therapy]" (page 1750, column 2). Ortel et al. teaches that other types of cells, which similarly accumulate more protoporphyrin after differentiation, are more photosensitive (abstract).

In view of the teachings of the prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to inhibit the proliferation of phaeochromocytoma cancer cells in a subject by treating the cells with NGF, providing the cells with ALA, and activating endogenous ALA-induced protoporphyrin, because Ortel et al. teaches the NGF-induced differentiation of the cells leads to accumulation of protoporphyrin, which the teachings of Ortel et al. suggest causes the cells to be more photosensitive. One of ordinary skill in the art would have been motivated at the time of invention to do so to treat a subject having phaeochromocytoma.

20. Claims 1-4, 7, 8, 12, 13, 26, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Momma et al. (*International Journal of Cancer* **72**: 1062-1069, 1997).

Momma et al. teaches hormonal modulation of androgen-dependent prostate cancers affects their metabolism, which could lead to altered synthesis and/or retention of protoporphyrin IX (page 1062, paragraph bridging columns 1 and 2). Momma et al. teaches LNCaP cells are an androgen-responsive, i.e., androgen-dependent prostate cancer cell line (page 1062, column 2). Momma et al. teaches pretreating LNCaP cells with 5α-dihydrotestosterone (DHT) causes a dose-dependent increase in the amount of protoporphyrin IX after exposure of the cells to 5-aminolevulinic acid (ALA) (abstract). Momma et al. teaches a relatively high concentration of DHT causes the cells to take up approximately 75% more ALA than a lower concentration, which difference accounts for the increased cellular content of protoporphyrin in the cells treated using the higher concentration (page 1066, column 2). Following the photoactivation of endogenous protoporphyrin, Momma et al. discloses the survival of the cells treated with the higher concentration of DHT decreases, as compared to the cells treated with the lower concentration (page 1068, column 1). Momma et al. teaches this effect is observed past the point when increased concentrations of DHT cause a reversal of initial growth stimulation by DHT (page 1066, column 2). Thus, even after the growth rate of the DHT-treated cells peaks and slows, protoporphyrin continues to accumulate in the cells. Momma et al. discloses the mechanism by which DHT causes this effect is not precisely known (page 1066, column 2), but Momma et al. discloses the growth rate of the cells does not correlate with the protoporphyrin content of the cells (page 1066, column 2). Momma et al. concludes, because "in an androgen-responsive prostate cancer cell line, the cellular content of PpPIX (and consequently phototoxicity) produced by exogenous administered ALA increased with pre-treatment of the cells with androgen", whereas "[n]o effect of hormones was observed in a non-responsive cell line or when the photosensitizer BPD was added [...,] the hormonal status of the patient may be a factor taken into account when planning the use of ALA-PDT as an adjuvant treatment after radical prostatectomy" (page 1068, column 2).

Although Momma et al. does not expressly teach that treating the androgen-dependent prostate cancer cells with DHT causes their differentiation, but Momma et al. does disclose androgen treatment can affect the metabolism of the cells, which could

lead to altered synthesis and/or retention of protoporphyrin IX by the cells. Since Momma et al. teaches accumulation of protoporphyrin by the cells is observed past the point when increased concentrations of DHT cause a reversal of initial growth stimulation, and therefore the growth rate of the cells does not correlate with the protoporphyrin content of the cells, the teachings of Momma et al. suggest the treatment causes the cells to differentiate.

At page 4, lines 19-22, the specification discloses the induction of differentiation by the action of an exogenous agent is exemplified by an increase in the photosensitivity of the cell. Therefore, because Momma et al. teaches androgen treatment of LNCaP cells causes an increase in the photosensitivity of the cells, the treatment of the cells induces the differentiation of those cells.

In view of the teachings of the prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to inhibit the proliferation of androgen-dependent prostate cancer cells in a subject by treating the cells with DHT, providing the cells with ALA, and activating endogenous ALA-induced protoporphyrin, because Momma et al. teaches even after the growth rate of the DHT-treated cells peaks and slows, protoporphyrin continues to accumulate in the cells, which causes the cells to be relatively more photosensitive. One of ordinary skill in the art would have been motivated at the time of invention to do so to treat a subject having androgen-dependent prostate cancer.

21. Claims 1-4, 7, 8, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schoenfeld et al. (*International Journal of Cancer* **56**: 106-112, 1994).

Schoenfeld et al. teaches increased accumulation of protoporphyrin by melanoma cells following exposure of the cells to the natural precursor 5-aminolevulinic acid (ALA) and dimethylsulfoxide (DMSO), a differentiation-inducing agent; see, e.g., the abstract, page 109, column 2, and page 110, column 1. Schoenfeld et al. discloses inducing the cells to differentiate and then providing the photosensitizer while the cells are in a state of induced differentiation achieves this effect; see, e.g., page 107, column

1. Schoenfeld et al. teaches photosensitization of the melanoma cells containing the higher protoporphyrin concentrations was effective even at low light doses (abstract). Schoenfeld et al. teaches after 5 minutes of illumination, complete cell destruction resulted (abstract). Schoenfeld et al. concludes, "[o]n the basis of the present results, we suggest 5-ALA-PDT [5-ALA-photodynamic therapy] may be developed for the treatment of skin and metastatic melanomas in appropriate conditions for porphyrin induction and photo-activation" (page 111, column 2).

For clarity, claim 1 recites providing a photosensitizer comprising a porphyrin. Claim 3 recites the method of claim 1 wherein the photosensitizer is administered to the subject, whereas claim 4 recites the method of claim 1 wherein a precursor of the photosensitizer is administered to the subject. As stated above, the prior art suggests administering to the subject ALA, which is actually a precursor of the photosensitizer protoporphyrin IX. The prior art does not suggest administering to the subject the photosensitizer. Nevertheless, claim 3 has been included in this rejection, because at page 3, line 19, the specification teaches the "photosensitizer" of claim 3 can be ALA.

In view of the teachings of the prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to inhibit the proliferation of melanoma cells in a subject by inducing the cells in the subject to differentiate by treating the cells with DMSO, providing the cells with ALA, and activating endogenous ALA-induced protoporphyrin, because Schoenfeld et al. teaches melanoma cells treated with DMSO contain relatively higher protoporphyrin concentrations, which causes the cells to be relatively more photosensitive, even at low light doses. Schoenfeld et al. teaches on the basis of their results, ALA-PDT may be developed for the treatment of skin and metastatic melanomas in appropriate conditions for porphyrin induction and photo-activation, so one of ordinary skill would have had a reasonable expectation of successfully developing such a regimen for treating a subject having melanoma. One of ordinary skill in the art would have been motivated at the time of invention to do so to treat a subject having melanoma.

Conclusion

22. No claims are allowed.

23. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. WO 98/30242 A2 teaches a method for in vitro diagnosis comprising admixing a body fluid or tissue with a photosensitizing agent and a differentiating agent, exposing the mixture to light, ascertaining the level of light emitted, and comparing the level to control levels. Malik et al. teaches induction of protoporphyrin biosynthesis and photodynamic inactivation of melanoma cells.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler, Ph.D. can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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